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March 14, 2002

The Honorable Christine Todd Whitman
Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Subject: Comments on the Industrial Health Foundation's HPV Test Plan for Cyclohexanol

Dear Administrator Whitman:

The following comments on the Industrial Health Foundation's (IHF's) test plan for cyclohexanol are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than nine million Americans.

Cyclohexanol is a basic industrial chemical and solvent used primarily in the production of nylon intermediates and in lacquers, paints, varnishes, degreasers, and plastics. Information on the toxicity of cyclohexanol exists for each SIDS endpoint. Despite the availability of data, including an Environmental Protection Agency (EPA) report on the developmental and reproductive toxicity of cyclohexanol, the IHF's test plan includes a proposal for a 90-day inhalation study (OECD TG 413) with rats. In addition, the consortium plans to retest this chemical for reproductive and developmental toxicity endpoints if adverse reproductive effects are seen in the repeat-dose study. This testing strategy involves the largest number of animals as well as studies with the longest duration, and does so without any justification. Conducting these repetitive tests on animals will do nothing to protect public health or the environment. These problems were also present in the IHF's previous test plan for cyclic anhydrides. In that test plan, the IHF proposed to conduct the 90-day repeat dose, reproductive, and developmental toxicity tests separately, with a blinding and corrosive chemical.

The IHF test plan for cyclohexanol specifically violates the following terms of the October 1999 Agreement among the EPA, industry, and health, animal protection, and environmental organizations:

1. In analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there is sufficient data, given the totality of what is known about a chemical, including human experience, that certain endpoints need not be tested.
2. Participants shall maximize the use of existing and scientifically adequate data to minimize further testing.

Our main objections to the test plan are:

- The IHF's test plan completely ignores the principles of the three R's (replacement, reduction, refinement) and the terms and spirit of the October 1999 Agreement.
- Empirical toxicity data on cyclohexanol are available and sufficient to characterize the hazards of

this solvent. In fact, the EPA has already assessed the existing information on reproductive and developmental toxicity and described it in detail in a document entitled *Evidence on the Developmental and Reproductive Toxicity of Cyclohexanol.*[1]

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The IHF's test plan includes a proposal for a 90-day inhalation study (OECD TG 413) with rats and a retesting of this chemical for reproductive and developmental toxicity endpoints, if adverse reproductive effects are seen in the repeat-dose study. This proposed testing scheme could result in the deaths of 1,280 animals if all three tests are done, compared to the 400 who would be killed in one combined OECD 422 test guideline, which the EPA recommends in the interest of reduction. Additionally, a subchronic 90-day inhalation study is carried out for a longer period and with more animals than the SIDS protocol for repeat toxicity via inhalation (OECD TG 412), in which studies are carried out for 14 or 28 days. As we stated in our previous comments to the IHF, dated August 15, 2001, the 90-day study is not even a part of the SIDS screening battery.

Empirical toxicity data on cyclohexanol are available and sufficient to characterize the hazards of this solvent. In fact, the EPA has already assessed the existing information on reproductive and developmental toxicity and described it in detail in a document entitled *Evidence on the Developmental and Reproductive Toxicity of Cyclohexanol.*[1]

According to the Occupational Safety and Health Administration (OSHA) as well as the American Conference of Government Industrial Hygienists (ACGIH), exposure to cyclohexanol is associated with eye and skin irritation, kidney and liver damage, and CNS effects. OSHA has already established 50 ppm as a safe concentration of cyclohexanol in air.

Gondry observed that oral administration of a 1% concentration of cyclohexanol inhibited the growth of male and female mice.[2]

A study by Tyagi *et al*. (1979) found that cyclohexanol exposure induced an infertility state. The investigators reported that 15 mg/kg of cyclohexanol given to the animals for 21 to 37 days caused testicular atrophy, the loss of type A spermatogonia, spermatocytes, and spermatozoa in gerbils and rats. The investigators also observed shrinkage of the seminiferous tubules and leydig cells. RNA, protein, sialic acid, and glycogen of testes, epidedymides, and seminal vesicles decreased.[3]

According to data from the ACGIH documentation on the threshold limits for cyclohexanol, pregnant and nonpregnant mice were given 0.1%, 0.5%, or 1.0 % cyclohexanol in the diet through gestation, lactation, and weaning for several generations. Growth and mortality of the animals were monitored. The 1.0% concentration produced a significant increase in mortality of the offspring during the 21 days after birth.[4]

Associated CNS effects include intoxication, lethargy, depression, and conjunctival congestion and irritation. One study in the literature reported that rats treated with 200 mg/kg cyclohexanol for up to 13 weeks did not appear to experience motor impairment, reduced coordination, or ataxia.[5]

Human subjects exposed to 100 ppm cyclohexanol for three to five minutes experienced irritation of the eyes, nose, and throat.[6] Human subjects given a 48-hour closed patch test with 4% cyclohexanol showed no evidence of irritation.[7]

Groth *et al*. conducted a toxicity study with frog embryos. Some observed abnormalities included edematous enlargement of the pericardial space, deformation of the skeleton and muscle apparatus, and retardation of body development.[8]

Cyclohexanol was evaluated in a study of dicyclohexyl phthalate. Cyclohexanol was given to twelve 30-day-old Sprague Dawley rats for seven days. It was associated with liver enlargement and testicular damage.[9]

Dixit *et al*. (1980) orally administered cyclohexanol to male rabbits. Significant reductions in relative testes and epididymal weights were observed in treated rabbits. A loss of type A spermatogonia, spermatocytes, spermatids, and spermatozoa were all reduced. In the epididymides of these animals, the luminal epithelium was reported to be reduced. The diameters of seminiferous tubules and Leydig cell nuclei were significantly reduced. Testicular and epididymal contents of protein, RNA, sialic acid, glycogen, and acid phophatase were all significantly reduced in treated animals.

These studies and others were all described in the California EPA document entitled *Evidence on the Developmental and Reproductive Toxicity of Cyclohexanol*.[1] Clearly, the existing information is sufficient to characterize the potential hazards associated with exposure to cyclohexanol. Studies have already reported adverse reproductive effects in animals dosed with this chemical. Conducting screening level tests is not likely to provide more definitive information its toxicity.

The IHF appears more interested in testing and retesting cyclohexanol for reproductive and developmental toxicity endpoints in the hopes that more equivocal results can be found to obfuscate the issue. The HPV program is a screening level program, not a vehicle for repetitive testing for the purposes of vindicating a chemical. The intention of the program is to identify possible hazards, and that has already been achieved for this chemical by available data. Conducting duplicative screening level tests is wholly inappropriate and unnecessary.

For all the reasons detailed above, it is imperative that the EPA not allow this testing plan to go forward.

Thank you for the opportunity to comment. I look forward to your response on this important issue. I can be reached at 202-686-2210, ext. 302, or *ncardello@pcrm.org*. Correspondence can be sent to my attention to PCRM, 5100 Wisconsin Ave., N.W., Suite 400, Washington, DC 20016.

Sincerely,

Nicole Cardello, M.H.S.
Staff Scientist

References

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